33. The vector of Claim 32, and further comprising an RSV promoter controlling said DNA sequence encoding endostatin and said DNA sequence encoding the secretion signal peptide of Ig-Kappa.

REMARKS

Claims 32 and 33 have been added in order to define specific embodiments of the claimed invention.

The present invention is directed to adenoviral vectors including a DNA sequence encoding endostatin.

In one embodiment, as defined in Claim 32, the adenoviral vector includes a DNA sequence encoding endostatin, and a DNA sequence encoding the secretion signal peptide of Ig-Kappa immediately 5' to the DNA sequence encoding endostatin. As defined in Claim 33, the adenoviral vector further comprises an RSV promoter controlling the DNA sequence encoding endostatin and the DNA sequence encoding the secretion signal peptide of Ig-Kappa.

Applicants have discovered that, if one administers to a host an adenoviral vector which includes a DNA sequence encoding endostatin and a DNA sequence encoding the secretion signal peptide of Ig-Kappa immediately 5' to the DNA sequence encoding endostatin, and preferably with an RSV promoter controlling both sequences, such a vector can provide for expression of endostatin in the host at effective therapeutic levels, such as from about 200 ng/ml to about 500 ng/ml, for example.

Claims 1-2, 4-7, 11-17, 21-24, 28 and 29 stand rejected under 35 U.S.C. 102(a) as being anticipated by Leboulch, et al. This rejection is respectfully traversed.

The present invention is directed to an adenoviral vector including a DNA sequence encoding endostatin. Such a vector may be administered to a host or to a cell in order to express endostatin in a host or in a cell, or may be administered to a host in order to treat a tumor in a host, or to treat colon cancer metastases in a host.

Leboulch discloses a method of inhibiting tumor growth in a human patient by administering a nucleic acid molecule which expresses an anti-angiogenic polypeptide, which may be endostatin. The nucleic acid molecule which expresses an anti-angiogenic polypeptide may be contained in an expression vector. Although Leboulch mentions that the nucleic acid molecule which expresses an anti-angiogenic polypeptide may be contained in an adenoviral vector, all actual examples in Leboulch are directed to retroviral vectors which include nucleic acid sequences encoding anti-angiogenic polypeptides. One skilled in the art is provided with no guidance regarding how to construct an adenoviral vector including a DNA sequence encoding endostatin. Thus, Leboulch does not enable one skilled in the art to construct Applicants' claimed adenoviral vector. Because Leboulch does not enable one skilled in the art to construct an adenoviral vector including a DNA sequence encoding endostatin, Leboulch does not anticipate Applicants' claimed adenoviral vector, nor does Leboulch render Applicants' claimed adenoviral vector obvious to one of ordinary skill in the art.

Applicants reserve the right to file a Declaration Under 37 CFR 1.131 to show reduction to practice of the claimed adenoviral vector prior to June 3, 1999, the publication date of Leboulch. The filing of such a Declaration is not to be construed, however, as an admission by Applicants or Applicants' attorneys that Claims 1, 2, 4, 7, 11-17, 21-24, 28 and 29 are anticipated by Leboulch under 35 U.S.C. 102(a) in the absence of such a Declaration.

It is therefore respectfully requested that the rejection under 35 U.S.C. 102(a) be reconsidered and withdrawn.

Claims 1-3 stand rejected under 35 U.S.C. 103 as being unpatentable over Leboulch, et al. taken with Blezinger, et al. This rejection is respectfully traversed.

Leboulch, as stated hereinabove, does not enable one of ordinary skill in the art to construct an adenoviral vector including a DNA sequence encoding endostatin. Thus, Leboulch does not render Applicants' claimed adenoviral vector obvious to one of ordinary skill in the art.

Blezinger discloses a plasmid which includes an endostatin gene and a sequence encoding the secretion signal for mouse Ig-Kappa. The plasmid is administered intramuscularly with a polyvinylpyrrolidone carrier. Blezinger, however, does not disclose or even remotely suggest to one of ordinary skill in the art an adenoviral vector including a DNA sequence encoding endostatin.

The combination of Leboulch and Blezinger, therefore, at best enables one skilled in the art to construct a plasmid which includes a nucleic acid sequence encoding

endostatin and a nucleic acid sequence encoding a secretion signal from the mouse Ig-Kappa chain. Such combination provides no guidance and not even the remotest suggestion to one of ordinary skill in the art as to how to construct an adenoviral vector including a DNA sequence encoding endostatin as claimed by Applicants. Therefore, the combination of Leboulch and Blezinger does not render Applicants' claimed adenoviral vector obvious to one of ordinary skill in the art.

Applicants reserve the right to file a Declaration under 37 CFR 1.131 in which Applicants will show reduction to practice of an adenoviral vector as defined in Claims 1 through 3 prior to June 3, 1999, the publication date of the Leblouch PCT application, and prior to April 1999, the publication date of Blezinger. The filing of such a Declaration is not to be construed as an admission by Applicants or Applicants' attorneys that Leboulch and Blezinger render Claims 1-3 obvious to one of ordinary skill in the art under 35 U.S.C. 103 in the absence of such a Declaration.

It is therefore respectfully requested that the rejection under 35 U.S.C. 103 be reconsidered and withdrawn.

Claims 4, 7-10, 14, 18-21 and 25-27 stand rejected under 35 U.S.C. 103 as being unpatentable over Leboulch, et al. and Blezinger, et al., and further in view of O'Reilly, et al. This rejection is respectfully traversed.

The combination of Leboulch and Blezinger, as noted hereinabove, does not even remotely suggest to one of ordinary skill in the art an adenoviral vector including a DNA sequence encoding endostatin. O'Reilly merely discloses isolated endostatin protein, which

inhibits endothelial cell proliferation and angiogenesis. O'Reilly does not disclose or even remotely suggest to one of ordinary skill in the art that endostatin may be given to an animal by administering an adenoviral vector which includes a DNA sequence encoding endostatin. Therefore, the combination of O'Reilly with Leboulch and Blezinger would not even remotely suggest to one of ordinary skill in the art an adenoviral vector including a DNA sequence encoding endostatin, and do not even remotely suggest to one of ordinary skill in the art that such a vector may be administered in an amount effective to provide expression of endostatin in an amount of up to 1,000,000 μg/ml, or at least 200 μg/ml, or from about 200 μg/ml to about 500 μg/ml. Leboulch, Blezinger, and O'Reilly, therefore, does not render Applicants' claimed adenoviral vector and methods of administering such vector to one of ordinary skill in the art, and it is therefore respectfully requested that the rejection under 35 U.S.C. 103 be reconsidered and withdrawn.

Claims 28-31 stand rejected under 35 U.S.C. 103 as being unpatentable over Leboulch, et al. and Blezinger, et al., and further in view of Kovesdi, et al. This rejection is respectfully traversed.

Leboulch and Blezinger do not disclose or even remotely suggest to one of ordinary skill in the art an adenoviral vector including a DNA sequence encoding endostatin. Kovesdi merely discloses replication deficient adenoviral vectors, and complementing cell lines for supplying adenoviral proteins necessary for the generation of adenoviral vector particles. Kovesdi, however, does not disclose or even remotely suggest to one of ordinary

skill in the art that the replication deficient adenoviral vectors include a DNA sequence encoding endostatin.

The combination of Leboulch, Blezinger, and Kovesdi, therefore, does not even remotely suggest to one of ordinary skill in the art Applicants' claimed method of expressing endostatin in a cell, such as a mammalian cell, such as A549 cells or Hep3B cells, by administering to a cell an adenoviral vector including a DNA sequence encoding endostatin. Therefore, the combination Leboulch, Blezinger, and Kovesdi does not render Applicants' claimed method of expressing endostatin in a cell obvious to one of ordinary skill in the art, and it is therefore respectfully requested that the rejection under 35 U.S.C. 103 be reconsidered and withdrawn.

Claims 4-27 stand rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for any and all methods of delivery in any and all hosts of an adenoviral vector comprising any and all DNA sequences encoding endostatin. This rejection is respectfully traversed.

In response, Applicants state that the Examiner has admitted that the specification is enabling for a method of treating a tumor or metastasis by a direct intratumor administration of an adenoviral vector comprising a full length cDNA sequence encoding murine endostatin for expression of said endostatin. Once one skilled in the art has been enabled to practice this embodiment of the invention, one skilled in the art would expect reasonably that an adenoviral vector including DNA sequences encoding endostatins other than murine endostatin could be constructed, and that such adenoviral vectors could be

administered by methods other than direct intratumor administration. The Examiner has provided no evidence, other than sheer speculation, which would indicate to those skilled in the art that adenoviral vectors including DNA sequences encoding endostatins other than murine endostatins could not be constructed, or that methods of administration other than direct intratumoral administration could not be employed. The Examiner, therefore, has not met her burden in showing that the specification does not provide an enabling disclosure. (*See* In Re Marzocchi, 169 U.S.P.Q. 367 (C.C.P.A. 1971), at 370.) For the above reasons and others, the specification provides an enabling disclosure, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn.

Regarding the rejections under 35 U.S.C. 112, second paragraph, Applicants assert that Claims 4, 11, 14, 21, and 28 do not omit essential steps. One of ordinary skill in the art would understand readily that if an adenoviral vector were administered to a host or to a cell, that upon administration, the adenoviral vector would be expected to express endostatin in the cell or in the host, and that if endostatin is expressed in the host, the endostatin expressed in the host may inhibit, prevent, or destroy the growth of tumors, such as colon cancer metastases, in the host. Therefore, Claims 4, 11, 14, 21, and 28, and the claims dependent thereon, point out particularly and claim distinctly the subject matter that Applicants regard as the invention, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112, second paragraph, be reconsidered and withdrawn.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,

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